Division of Anti-Infective and Ophthalmology Products Advisory Committee Meeting

Rejena (sodium hyaluronate ophthalmic solution) 0.18%

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Applicant Information

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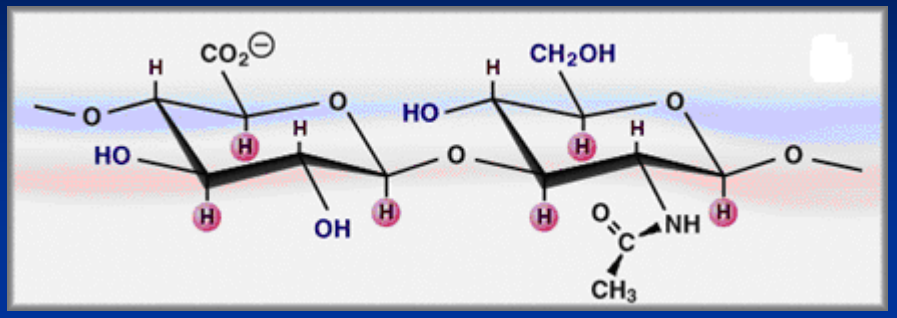
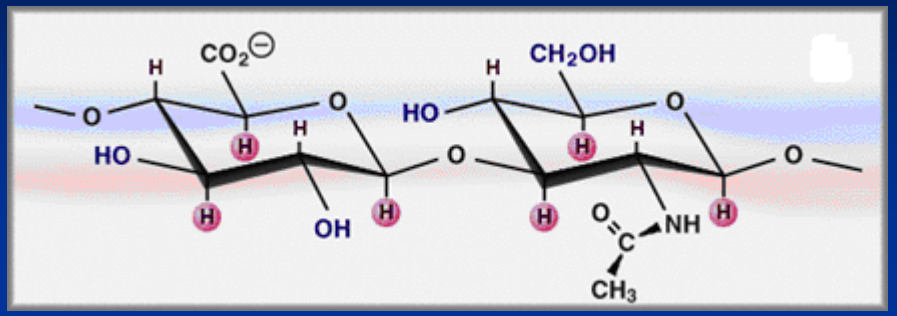
Introduction and Background



- REJENA (sodium hyaluronate ophthalmic solution), 0.18%
  - Sterile ophthalmic solution
  - Empirical formula for sodium hyaluronate is $(C_{14}H_{20}O_{11}N_1Na_1)_n$.
  - Hyaluronic acid, Hyaluronic acid sodium salt or Hyaluronan.

- Sodium hyaluronate is a polymer produced by bacterial fermentation.
  - Fermentation process allows for a high degree of control for achieving a relatively narrow range of molecular weights.
  - Intrinsic viscosity gives sodium hyaluronate characteristic long residence time on the surface of the eye.

Introduction and Background



- Sodium hyaluronate is approved as a Class 3 medical device in the US, as a surgical viscoelastic (i.e., Healon).

- Tested formulation is approved in 40 other countries and is currently marketed in 28 countries, as Vismed, Vislube and Hylovis in Europe, Australia and parts of Asia since January 1998.

Applicant Proposed Indication

- For the treatment of the signs and symptoms of dry eye disease.

Other Available Treatments

- Restasis (cyclosporine ophthalmic emulsion) 0.05% is approved to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivits sicca.

- There are many over the counter demulcent products to manage symptoms of dry eye disease.

Regulatory Requirement of Evidence of Effectiveness

- FD & C Act [21 USC §355 section 505 (d)]:
  - Substantial evidence is required to establish a drug's effectiveness.
  - Substantial evidence consists of adequate and well-controlled (AWC) investigations.

Clinical Safety and Efficacy Studies Conducted with Sodium hyaluronate ophthalmic solution

- Ten published clinical trials (512 subjects)
  - Three studies did not use Vismed
  - Three were not controlled
  - Three were open label

AWC Clinical Study with Vismed (sodium hyaluronate ophthalmic solution, 0.18%) Prior to Design of Study RP-001

Study No.	Primary Efficacy Endpoint	Study Design	Main Entry Criteria	Number Pts Treated, Treatment	Duration of Treatment
Baudouin 2005 SVS20-99-04 France (2002 – 2005)	***Objective: Change from baseline in corneal fluorescein staining summed score on Day 28*** ***Subjective: Change VAS summed score on Day 28***	***Phase 3 multicenter, randomized, controlled, double-masked, parallel-group study***	Bilateral moderate dry eye disease or moderate dry eye due to Sjögrens syndrome	151 randomized 74 SH 0.18% 77 saline 1 drop of OU at least TID and up to 8 X per day as needed	28 days

Clinical Studies Submitted in NDA 22-358
Considered Adequate and Well Controlled by FDA

Study No.	Primary Efficacy Endpoint	Study Design	Main Entry Criteria	Number Pts Treated, Treatment	Duration of Treatment
Baudouin 2005 SVS20-99-04 **France (2002 – 2005)**	***Re-analysis of original data*** ***Using redefined endpoints, the same endpoints as in Study RP-001***	***Phase 3 multicenter, randomized, controlled, double-masked, parallel-group study***	Bilateral moderate dry eye disease or moderate dry eye due to Sjögrens syndrome	151 randomized 74 SH 0.18% 77 saline 1 drop OU at least TID and up to 8X per day as needed	28 days
RP-001 River Plate Biotechnology **US (2006 – 2008)**	Objective: Change from baseline at Day 7 in lissamine green staining Subjective: Change from baseline at Day 7 in global symptom frequency	***Phase 3 multicenter, randomized, controlled, double-masked, parallel-group study***	At least a 3-month documented history of dry eye in both eyes diagnosed as dry eye disease, KCS, or due to Sjögrens syndrome	444 randomized 221 SH 0.18% 223 vehicle 1-2 drops of either product OU at least TID and up to 6X per day as needed	14 days

Baudouin 2005 (SVS20-99-04)

- Multicenter (18), randomized, controlled, double-masked, parallel-group study
- Subjects with bilateral moderate dry eye disease or moderate dry eye due to Sjögrens syndrome
- Treatments: Sodium Hyaluronate ophthalmic solution 0.18% and saline;
  - 1 drop OU at least TID and up to 8 times per day
- Four visits over 28 days
  - Visit 1 - Selection (Day -12 to -4)
  - Visit 2 - Inclusion (Day 0)
  - Visit 3 (Day 7)
  - Visit 4 (Day 28)

Baudouin 2005 (SVS20-99-04)

Key Inclusion Criteria

- ≥ 18 years with at least 3 month documented moderate dry eye due to Sjogren's syndrome
- Experiencing at least 2 symptoms of bilateral dry eye – soreness, scratchiness, dryness, grittiness and burning (at least occurring often and at least rated 40 mm on VAS)
- At least 3 out of 4 objective parameters:
  - Schirmer test ≤ 10 mm wetting / 5 min for each eye
  - BUT ≤ 10 sec for each eye
  - Fluorescein staining ≥ 3 (of 12) for each eye
  - Lissamine green staining ≥ 3 (of 12) for each eye

Baudouin 2005 (SVS20-99-04)

Key Exclusion Criteria

- Unilateral dry eye
- Severe dry eye syndrome
  - Fluorescein staining depth score ≥ 3 of 4 and/or
  - Severe bulbar conjunctival hyperemia (score of 4) and/or
  - Severe limbal hyperemia (score of 4) and/or
  - Severe palpebral conjunctival observation (score of 4) and/or
  - Severe blepharitis
- Ocular surgery or trauma in previous 4 months
- Abnormal nasolacrimal drainage apparatus
- Permanent occlusion of lacrimal puncta in either eye
- Temporary punctal occlusion within 2 months

Baudouin 2005 (SVS20-99-04)

Baudouin's Original Efficacy Endpoints

- Percent change from baseline in Corneal Fluorescein Score at Day 28
  - Summed over both eyes
- Percent change from baseline in Final Visual Analogue Scale (VAS) Sum Score at Day 28
  - Sum of 5 symptoms (soreness, scratchiness, dryness, grittiness and burning for both eyes) on VAS scale at the final visit

Baudouin 2005 (SVS20-99-04)

Demographic Data (ITT Population)

	Vismed n=73	Saline n=77	p-value
Age (years)			0.9038
Mean	61.4	61.7	
SD	14.0	12.5	
Gender, N (%)			0.8280
Male	13 (17.8%)	12 (15.6%)	
Female	60 (82.2%)	65 (84.4%)	

Baudouin 2005 (SVS20-99-04)

Disposition of Subjects Randomized to Treatment (ITT Population)

	Vismed (N=74)	Saline (N=77)	Overall (N=151)
Completed, N (%)	71 (95.9)	74 (96.1)	145 (96.0)
Subjects Withdrawn Early	3 (4.1)	3 (3.9)	6 (4.0)
Adverse Event	0	1 (1.3)	1 (0.7)
Patient Decision	1 (1.4)	0	1 (0.7)
Lack of efficacy	2 (2.7)	2 (2.6)	4 (2.6)

Baudouin 2005 (SVS20-99-04)

Subjects Discontinued from Treatment or Study
Safety Population

Reason for Discontinuation	Treatment	Center Number	Patient Number
Adverse event – vertigo, malaise, palpitations	Saline	7	7005
Adverse event – burning after instillation	SVS20	10	10002
Adverse event – edema of external canthus	Saline	17	22003
Lack of efficacy	Saline	8	8003
Lack of efficacy	SVS20	10	10006 [a]
Withdrawal of consent	SVS20	14	14004

a Patient did not return for any follow-up visits due to "lack of efficacy"

Baudouin 2005 (SVS20-99-04)

Analysis Populations

	SVS20 (N=74)	Saline (N=77)
Randomized	74 (100.0%)	77(100.0%)
ITT Data Set [a]	73 (98.6%)	77 (100.0%)
PP Data Set [b]		
Day 0	70 (95.0%)	73 (94.8%)
Day 7	73 (98.6%)	76 (98.7%)
Day 28	68 (91.9%)	73 (94.8%)
Safety Data Set [c]	73 (98.6%)	77 (100.0%)

N= No. of subjects in the ITT population in each treatment group, which is used as the denominator for all percentage calculations.

a All patients who had at least one administration of the allocated product, at least one follow-up visit for the primary efficacy criteria and no severe protocol deviation.

b All patients of the ITT data set without major protocol deviations

c All patients who had at least one administration of the allocated product.

Baudouin 2005 Original Analysis and Submitted Clinical Study Report (CSR)
Reliability of data

- The Baudouin 2005 CSR presented summary tables with descriptive statistics calculated for *percent change from baseline* for the primary and secondary endpoints.

- However, the p–values presented for two of the secondary endpoints (the lissamine green staining score and the symptom frequency score) were derived from *absolute change from baseline* rather than percent change from baseline).

Baudouin 2005 failed its primary subjective endpoint

Percent Change from baseline in the symptom intensity score at Day 28
ITT Population with LOCF

	REJENA (N=73)	Saline (N=77)	Difference (ANCOVA)	2-side p-value
n Mean (SD)	72 -35.95 (31.68)	77 -26.80 (43.17)	**-8.74**	**Primary Analysis** **Wilcoxon** **0.2665** ***(0.2674 CSR)*** **Sensitivity Analysis** ANCOVA 0.1633
95% CI	(-43.39 , -28.50)	(-36.60 , -17.00)	(-21.07 , 3.59)	
Median	-40.4	-31.9		
25^{th}, 75^{th} Quartile	-51.8, -20.7	-57.9, -3.8		
Range	-99, 46.4	-100, 171.6		

Note: baseline values were not carried forward. The percent change was treated as missing if the baseline value was zero. There were no zero baseline values for this endpoint.

Baudouin 2005 failed its primary objective endpoint

Percent Change from baseline in the fluorescein staining score at Day 28
ITT Population with LOCF

	REJENA (N=73)	Saline (N=77)	Difference (ANCOVA)	2-side p-value
n Mean (SD)	69 -44.89 (43.05)	75 -32.87 (39.52)	**-12.08**	**Primary Analysis** **Wilcoxon** **0.0649** ***(0.0558 CSR)*** **Sensitivity Analysis** ANCOVA 0.0802
95% CI	(-55.23 , -34.55)	(-41.97 , -23.78)	(-25.63 , 1.47)	
Median	-25	-25		
25^{th}, 75^{th} Quartile	-100, -14.3	-62.5, 0		
Range	-100, 36.4	-100, 33.3		

Note: baseline values were not carried forward. The percent change was treated as missing if the baseline value was zero. Two subjects in the saline group and three subjects in the REJENA groups had a zero baseline value.

Baudouin 2005: results of select secondary subjective endpoint

Percent Change from baseline in the symptom frequency score at Day 28
ITT Population with LOCF

	REJENA (N=73)	Saline (N=77)	Difference (ANCOVA)	2-sided p-value
n Mean (SD)	72 -34.86 (26.38)	77 -22.83 (34.68)	**-12.19**	**Primary Analysis** **Wilcoxon** **0.0185** ***(0.0070 CSR)*** **Sensitivity Analysis** ANCOVA 0.0184
95% CI	(-41.06 , -28.66)	(-30.70 , -14.96)	(-22.29 , -2.09)	
Median	-37.5	-25		
25^{th}, 75^{th} Quartile	-50, 21.1	-44.4, 0		
Range	-100, 33.3	-100, 87.5		

Note: baseline values were not carried forward. The percent change was treated as missing if the baseline value was zero. There were no zero baseline values for this endpoint.

Baudouin 2005: results of select secondary objective endpoint

Percent change from baseline in the lissamine green staining score at Day 28

ITT Population with LOCF

	REJENA (N=73)	Saline (N=77)	Difference (ANCOVA)	2-side p-value
n Mean (SD)	65 -41.18 (31.24)	68 -22.97 (39.60)	**-18.43**	**Primary Analysis** **Wilcoxon** **0.0062** ***(0.0014 CSR)*** **Sensitivity Analysis** ANCOVA 0.0037
95% CI	(-48.92 , -33.44)	(-32.56 , -13.38)	(-30.75 , -6.10)	
Median	-41.7	-28.6		
25th, 75th Quartile	-66.7, -25	-50, 0		
Range	-100, 33.3	-88.9, 120		

Note: baseline values were not carried forward. The percent change was treated as missing if the baseline value was zero. Nine subjects in the saline group and seven subjects in the REJENA groups had a zero baseline value.

Presubmission Regulatory Activity

Pre-NDA Meeting – August 2007

- Could a multiplicity adjustment be applied to Baudouin 2005 secondary endpoints to allow it and Study RP-001 to constitute two studies in support of an NDA?

Presubmission Regulatory Activity

Pre-NDA Meeting – August 2007

- Agency Response
  - Baudouin 2005 failed its primary endpoint.
  - "Adjusting for multiplicity for the secondary endpoint has no statistical basis after the primary endpoint failed… the type I error cannot be controlled in any secondary analysis…"
  - Valid statistical inference on the secondary endpoints can not be drawn. Results of secondary endpoints should be treated as exploratory.

Presubmission Regulatory Activity

Pre-NDA Meeting – August 2007

- Agency Response
  - However, because the secondary endpoints showed differences we were willing to review the post hoc analysis as part of an application.
  - A robust p-value for the primary efficacy endpoint in Study RP-001 is expected.
  - Totality of the evidence submitted will be reviewed.

Study RP-001

- Multicenter, randomized, vehicle-controlled, double-masked parallel group study
- Subjects with at least a 3 month documented history of dry eye in both eyes.
- Diagnosed as dry eye disease, KCS, or due to Sjogren's syndrome
- Treatments: REJENA and vehicle;
  - 1 drop OU at least TID and up to 6 times per day
- Four visits over 14 days
  - Visit 1 – Screening (Day -7 to -5)
  - Visit 2 – Baseline (Day 0)
  - Visit 3 – Follow up (Day 7)
  - Visit 4 – Follow up (Day 14)

Study RP-001
Key Inclusion Criteria

- ≥ 18 years with at least a 3 month documented history of dry eye in both eyes (dry eye, KCS, Sjogren's)
- At least 2 symptoms of dry eye (soreness, scratchiness, dryness, grittiness, and burning)
  - Rated as ≥ 2 (often) on the symptom frequency scale
  - Scored as ≥ 50 mm on VAS
- The following objective parameters of dry eye:
  - Corneal fluorescein staining total score of ≥ 3
  - Lissamine green staining total score of ≥ 3
- Able to refrain from artificial tears during study
- No Restasis for 4 weeks prior to screening and during study

Study RP-001

Key Exclusion Criteria

- Ocular surgery or trauma within 4 months prior to screening.
- Abnormality of nasolacrimal drainage apparatus
- Punctal occlusion or diathermy within 3 months prior to screening
- Active eye inflammation not due to KCS (e.g., iritis, scleritis)
- Unilateral dry eye

Study RP-001
Efficacy Endpoints

- Change from baseline in Lissamine Green Staining at Day 7
  - Measuring cornea, nasal conjunctiva, and temporal conjunctiva.
- Change from baseline in Global Symptom Frequency at Day 7
  - Sum of 5 symptoms (soreness, scratchiness, dryness, grittiness, and burning)

Study RP-001

Demographic Data (ITT Population)

	REJENA n=221	Vehicle n=223	Total N=444
Age (years)			
Mean	**60.7**	**62.2**	**61.5**
SD	**12.6**	**14.8**	**13.7**
Median	**61.0**	**64.0**	**62.0**
Min, Max	**25, 85**	**21, 92**	**21, 92**
Gender, N (%)			
Female	**172 (77.8%)**	**161 (72.2 %)**	**333 (75.0%)**
Race, N (%)			
White	**192 (86.9 %)**	**188 (84.3 %)**	**380 (85.6 %)**
Black / African American	**20 (9.0%)**	**30 (13.5 %)**	**50 (11.3 %)**
American Indian / Alaskan Native	**3 (1.4 %)**	**2 (0.9 %)**	**5 (1.1 %)**
Other	**5 (2.3 %)**	**3 (1.3 %)**	**8 (1.8 %)**

Study RP-001

Disposition of Subjects Randomized to Treatment (ITT Population)

	REJENA (N=221)	Vehicle (N=223)
Completed, N (%)	217 (98.2)	219 (98.2)
Subjects Withdrawn Early	4 (1.8)	4 (1.8)
Adverse Event	2 (0.9)	1 (0.4)
Subject withdrew consent	1 (.05)	2 (0.9)
Protocol violation	0	0
Lost to Follow-up	1 (0.5)	1 (0.4)

Study RP-001

Subjects Discontinued from Treatment or Study
Safety Population

Reason for Discontinuation	Treatment	Investigator Number	Patient Number
AE – Benign colonic mass	Vehicle	0029	29020
AE – Blurred vision	REJENA	0039	39020
AE – Ocular hyperemia, viral conjunctivitis	REJENA	0039	39024
Lost to follow-up	Vehicle	0034	34029
Lost to follow-up	REJENA	0034	34020
Subject withdrew consent	Vehicle	0018	18053
Subject withdrew consent	Vehicle	0049	49001
Subject withdrew consent	REJENA	0018	18067

Study RP-001

Analysis Populations

	REJENA (N=221)	Vehicle (N=223)
Randomized	221 (100.0%)	223(100.0%)
ITT population	221 (100.0%)	223 (100.0%)
m ITT population	221 (100.0%)	221 (99.1%)
PP population	218 (98.6%)	219 (98.2%)
Safety population	221 (100.0%)	222 (99.6%)

Study RP-001

Randomized Subjects not included in the Per Protocol Population

Protocol violation	Treatment Group	Investigator Number	Patient Number
Lost to F/U - No post baseline visits	Vehicle	0034	34029
Reduced screening period (4 days)	Vehicle	0049	49013
Did not administer any study drug	Vehicle	0049	49001
Reduced screening period (4 days)	Vehicle	0073	73004
Did not have ≥ 2 global symptom frequency scores ≥ 2 at BL.	REJENA	0019	19030
Did not have ≥ 2 global symptom intensity scores ≥ 50 mm at BL.	REJENA	0034	34020
Reduced screening period (4 days)	REJENA	0044	44001

Study RP-001

Change from baseline in the symptom frequency score at Day 7

Marginally statistically significant results of the primary subjective endpoint

ITT Population with LOCF

	REJENA (N=221)	Vehicle (N=223)	Difference (ANCOVA)	2-side p-value
Mean (SD)	-1.74 (2.78)	-1.13 (2.62)	-0.57	Primary Analysis Wilcoxon 0.0497
95% CI	(-2.11 , -1.37)	(-1.48 , -0.78)	(-1.05 , -0.09)	
Median	-1	-1		Sensitivity Analysis ANCOVA 0.0193
25th, 75th Quartile	-3, 0	-3, 0		
Range	-11, 4	-8, 9		

Note: baseline values were carried forward if there was no post-baseline measurement.

Study RP-001

Change from baseline in lissamine green staining score at Day 7

Marginally statistically significant results of the primary objective endpoint

ITT Population with LOCF

	REJENA (N=221)	Vehicle (N=223)	Difference (ANCOVA)	2-side p-value
Mean (SD)	-1.05 (2.01)	-0.66 (1.79)	-0.34	Primary Analysis Wilcoxon 0.0502
95% CI	(-1.32 , -0.79)	(-0.90 , -0.42)	(-0.68 , -0.01)	
Median	-1	0		Sensitivity Analysis ANCOVA 0.0432
25^{th}, 75^{th} Quartile	-2, 0	-2, 0		
Range	-9, 6	-7, 8		

Note: baseline values were carried forward if there was no post-baseline measurement.

Study RP-001

Change from baseline in symptom frequency score at Day 14

ITT Population with LOCF

	REJENA (N=221)	Vehicle (N=223)	Difference (ANCOVA)	2-side p-value
Mean (SD)	-2.39 (2.91)	-2.05 (2.92)	-0.31	Primary Analysis Wilcoxon 0.3136 Sensitivity Analysis ANCOVA 0.2536
95% CI	(-2.78 , -2.01)	(-2.44 , -1.67)	(-0.84 , 0.22)	
Median	-2	-2		
25^{th}, 75^{th} Quartile	-4, -1	-4, 0		
Range	-11, 4	-10, 7		

Note: baseline values were carried forward if there was no post-baseline measurement.

Study RP-001

Change from baseline in lissamine green staining score at Day 14

ITT Population with LOCF

	REJENA (N=221)	Vehicle (N=223)	Difference (ANCOVA)	2-side p-value
Mean (SD)	-1.45 (1.91)	-1.05 (1.81)	-0.35	Primary Analysis Wilcoxon 0.0461
95% CI	(-1.70 , -1.20)	(-1.29 , -0.81)	(-0.68 , -0.02)	
Median	-1	-1		Sensitivity Analysis ANCOVA 0.0360
25^{th}, 75^{th} Quartile	-3, 0	-2, 0		
Range	-8, 3	-7, 5		

Note: baseline values were carried forward if there was no post-baseline measurement.

Two AWC Studies in NDA 22358 – *Baudouin 2005 and Study RP-001*

- Baudouin 2005

  Reliability of data:

  - The Baudouin 2005 CSR presented summary tables with descriptive statistics calculated for *percent change from baseline* for the primary and secondary endpoints.
  - The p−values presented in those tables were derived from *absolute change from baseline* rather than percent change from baseline for two secondary endpoints (the lissamine green staining score and the symptom frequency score).
  - Audit of data not possible.
    - Conducted in France in 2002-2005; not conducted under an IND.

Two AWC Studies in NDA 22358 – *Baudouin 2005 and Study RP-001*

- Baudouin 2005
  - Failed in its primary endpoints.
  - Valid statistical inference on the secondary endpoints could not be drawn. As stated in the statistical analysis plan, results of the secondary endpoints should be treated as exploratory.

Two AWC Studies in NDA 22358 – *Baudouin 2005 and Study RP-001*

- Study RP-001
  - Designed based on the results of the secondary endpoints from Baudouin 2005.
  - Study RP-001 shows a statistically significant treatment effect of REJENA over vehicle, but the p-values are not robust (i.e. p-values considerably less than 0.05).
  - FDA anticipated a clinically and statistically robust treatment effect from this study to support an NDA as was communicated prior to its conduct.

Integrated Review of Safety

Exposure to Sodium Hyaluronate in Key Studies of Dry Eye Disease

Study	Number of Patients/Subjects (REJENA Group)	Duration of treatment	Comparator(s)
Baudouin 2001 SVS20-99-02	11 (SVS20 TID)	56 days	Celluvisc
Baudouin 2005 SVS20-99-04	74 (SVS20 TID)	28 days	Saline
Study RP-001	221 SH 0.18% TID	14 days	Vehicle

Major Safety Results

Safety Population

- No deaths
- Nonfatal Serious Adverse Events
  - Study RP-001
    - Intestinal mass diagnosed (Vehicle)
    - Viral gastroenteritis (Vismed)

Major Safety Results

Subjects Discontinued from Treatment or Study

Study RP-001 - Safety Population

Reason for Discontinuation	Treatment	Investigator Number	Patient Number
AE – Benign colonic mass	Vehicle	0029	29020
AE – Blurred vision	REJENA	0039	39020
AE – Ocular hyperemia, viral conjunctivitis	REJENA	0039	39024
Lost to follow-up	Vehicle	0034	34029
Lost to follow-up	REJENA	0034	34020
Subject withdrew consent	Vehicle	0018	18053
Subject withdrew consent	Vehicle	0049	49001
Subject withdrew consent	REJENA	0018	18067

Major Safety Results

Subjects Discontinued from Treatment or Study

Baudouin 2005 - Safety Population

Reason for Discontinuation	Treatment	Center Number	Patient Number
Adverse event – vertigo, malaise, palpitations	Saline	7	7005
Adverse event – burning after instillation	REJENA	10	10002
Adverse event – edema of external canthus	Saline	17	22003
Lack of efficacy	Saline	8	8003
Lack of efficacy	REJENA	10	10006 [a]
Withdrawal of consent	REJENA	14	14004

a Patient did not return for any follow-up visits due to "lack of efficacy"

Ocular Adverse Events Reported by Greater than 1% of Subjects Across Studies (Safety Population)

System Organ Class Preferred Term	Study SVS20-99-04 (Baudouin 2005)		Study RP-001		Total Studies REJENA (N=305)
	REJENA (n=74)	Saline (n=77)	REJENA (n=221)	Vehicle (n=222)	
Eye Disorders					
Dry eye	0	0	18 (8.1%)	14 (6.3%)	18 (5.9%)
Eye pain	0	0	13 (5.9%)	7 (3.2%)	13 (4.3%)
Eye irritation	2 (2.7%)	0	4 (1.8%)	5 (2.3%)	6 (2.0%)
Foreign body sensation in eyes	0	0	5 (2.3%)	7 (3.2%)	5 (1.6%)
Visual acuity reduced	0	0	4 (1.8%)	6 (2.7%)	4 (1.3%)
Eye pruritus	0	0	4 (1.8%)	4 (1.8%)	4(1.3%)
Vision blurred	0	0	4 (1.8%)	0	4 (1.3%)
Ocular hyperemia	0	0	3 (1.4%)	3 (1.4%)	3 (1.0%)
Eyelid margin crusting	0	0	3 (1.4%)	1 (0.5%)	3 (1.0%)

N, No. of subjects in the safety population, SH, sodium hyaluronate

a Includes SVS20-99-02, in which no AEs were reported (N=10 in the active treatment group).

Notes: AEs were coded using MedDRA Version 10.0. AEs are ranked in order of incidence (≥ 1%) across

Postmarketing Experience

Adverse Event	Number of reports
Burning sensation	16
Hypersensitivity / intolerance	13
Eye reddening	5
Foreign body sensation	1
Eye injury	1
Local swelling	1
Other	1
Total	**38**

- 8.33 MM boxes (of 20 monodose units) sold from Jan 1998 to March 31, 2008
- Estimated 2.8 MM patients used the product during this period

Questions for the Advisory Committee

- Do you think adequate safety and efficacy for REJENA (sodium hyaluronate ophthalmic solution) 0.18% has been demonstrated for the treatment of the signs and symptoms of dry eye disease?
- If yes, on which study(ies) are you basing your decision?
- If not what additional study(ies) should be performed? Do you have any suggestions regarding trial design?
- Do you have any suggestions concerning the proposed draft labeling of the product?